Prognosis of malignant pheochromocytoma and paraganglioma (MAPP-Prono study): an ENS@T retrospective study

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Abstract: Background Malignant pheochromocytoma and paraganglioma (MPP) are characterized by prognostic heterogeneity. Our objective was to look for prognostic parameters of overall survival in MPP patients. Patients and Methods Retrospective multicentric study of MPP characterized by a neck-thoraco-abdomino-pelvic CT or MRI at the time of malignancy diagnosis in European centers between 1998 and 2010. Results We included 169 patients from 18 European centers. Main characteristics of MPP patients were: primary pheochromocytoma in 53% of patients, tumor or hormone-related symptoms in 57% or 58% of cases, positive plasma or urine hormones in 81% of patients, identification of a mutation in SDHB in 42 % of cases. Metastatic sites included the bone (64%), lymph node (40%), lung (29%) and liver (26%); mean time between initial and malignancy diagnosis was 43 months (0-614). Median follow-up was 68 months and median survival 6.7 years. Using univariate analysis, better survival was associated with head and neck paraganglioma, age <40 years, metanephrines <5-fold the upper limits of the normal range and low proliferative index. In multivariate analysis, hypersecretion (Hazard Ratio 3.02[1.65-5.55]; p:0.0004) was identified as independent significant prognostic factors of worst overall survival. Conclusions Our results do not confirm SDHB mutations as a major prognostic parameter in MPP and suggest additional key molecular events involved in MPP tumor progression. Aside from SDHB mutation, the biology of aggressive MPP remains to be understood.

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Background: Malignant pheochromocytoma and paraganglioma (MPP) are characterized by prognostic heterogeneity. Our objective was to look for prognostic parameters of overall survival in MPP patients.
Patients and Methods: Retrospective multicentric study of MPP characterized by a neck-thoraco-abdomino-pelvic CT or MRI at the time of malignancy diagnosis in European centers between 1998 and 2010.
Results: We included 169 patients from 18 European centers. Main characteristics of MPP patients were: primary pheochromocytoma in 53% of patients, tumor or hormone-related symptoms in 57% or 58% of cases, positive plasma or urine hormones in 81% of patients, identification of a mutation in *SDHB* in 42 % of cases. Metastatic sites included the bone (64%), lymph node (40%), lung (29%) and liver (26%); mean time between initial and malignancy diagnosis was 43 months (0-614). Median follow-up was 68 months and median survival 6.7 years. Using univariate analysis, better survival was associated with head and neck paraganglioma, age <40 years, metanephrines <5-fold the upper limits of the normal range and low proliferative index. In multivariate analysis, hypersecretion (Hazard Ratio 3.02[1.65-5.55]; *p*:0.0004) was identified as independent significant prognostic factors of worst overall survival.
Conclusions: Our results do not confirm *SDHB* mutations as a major prognostic parameter in MPP and suggest additional key molecular events involved in MPP tumor progression. Aside from *SDHB* mutation, the biology of aggressive MPP remains to be understood.

Retrospective study that identifies hormonal hypersecretion as independent significant prognostic factors of worst overall survival while SDHB mutations have no prognostic impact.

Introduction

Pheochromocytoma and paraganglioma are rare neuroendocrine chromaffin tumors located at adrenal or extra-adrenal sites and defined as malignant by the World Health Organization (WHO) by the occurrence of metastases in non-chromaffin organs (1). Malignant pheochromocytoma and paraganglioma (MPP) incidence is less than one case per million population per year (2). MPP are characterized by their heterogeneity including primary site location, genetic predisposition, hormonal secretion and metastatic organs (3). In addition, we recently demonstrated that half of MPP patients have stable disease at one year without any therapeutic intervention (4). Finally, heterogeneous survival has been described in the literature ranging from 40 to 77% at five year diagnosis (5–7) as well as heterogeneous progression free survival ranged from 4 to 36 months in therapeutic trials (8–11).

Pheochromocytoma and paraganglioma occurs as part of inherited syndrome in 40 % of case with up to 12 genes found related to this disease in the past two decades (12). Germline mutations in succinate deshydrogenase subunit B (*SDHB*) have been associated with higher rate of metastatic disease as well as rare mutations in *FH*, *MAX* and *SLC25A11* (13–17). Ten years ago, we previously reported that the presence or absence of *SDHB* mutation was associated with distinct median survival of 42 or 244 months in adults (5). The presence of the *SDHB* mutation was also associated with a low metastases-free survival in a pediatric series (18). Nevertheless these results were not confirmed in more recent reports (19,20). In

addition, other prognostic factors have been highlighted including age (7,19,21), extra-adrenal location (7,22–24), primary tumor size (7,19,22,24) or synchronous metastatic disease (7,19–21).

In this study, we retrospectively looked for prognostic factors of overall survival in a large series of patients with MPP followed up within the European Network for the Study of Adrenal Tumors (ENS@T).

Patients and Methods

Patients

The medical files of MPP patients, followed up between January 1998 and December 2010 were reviewed in 18 centers of ENS@T. Clinical data were entered in the ENS@T database by each center and then data were extracted and reviewed by one investigator (SH). An informed consent was obtained from all patients. Patients with the following criteria were included in the MAPP-Prono study (MetAstatic Pheochromocytoma and Paraganglioma PRONOstic study): 1. Confirmed diagnosis of MPP (including pheochromocytoma, abdominal, thoracic or head and neck paraganglioma) as defined by the presence of distant metastasis between 1998 and 2010; 2. Neck-Thoracic-abdomen-pelvic CT (TAP CT) performed within 4 months of metastasis diagnosis 3. Entire follow-up in the center. Exclusion criteria were: 1. Benign pheochromocytoma and paraganglioma; 2. Patients with venous or loco-regional or proximal lymph node spread, only.

The following parameters were recorded at the time of first TAP CT in the metastatic setting: gender, age, genetic status of dedicated genes including *SDHB* mutation analysis according to available guidelines at the time of patient management, location and size of the primary tumor, metastatic sites (bone, lymph nodes, lung, and liver), presence of hormone- or tumor-related symptoms, chromogranin A and total metanephrine levels, the mitotic count and Ki67 and the interval between the initial diagnosis and that of metastasis. Hormonal secretion was defined as elevated chromogranin A and/or metanephrines (i.e. 2-fold the upper limits of the normal range). Causes of death, related or not to MPP and status at last follow-up were recorded. The description and cut-off values of each parameter as well as the number of patients evaluable for each parameter are given in Table 1.

Statistical analysis

Quantitative values are reported as means +/- standard deviations (SD) or median [IQR] and categorical variables as percentages. Differences according to patients' characteristics were assessed using the chi-2 test or non-parametric Mann Whitney U-tests. A p value < 0.05 was considered significant. The primary endpoint of the study was overall survival (OS) defined by time from diagnosis of MPP (first thorax-abdomen or head and neck CT in the metastatic setting) (time zero: T0) to death by any cause. Specific survival was also analyzed. OS was estimated using Kaplan-Meier curves. Prognostic factors for OS were evaluated using the log-rank test in univariate analysis. Factors validated in univariate analysis were further tested in multivariate analysis. Results are reported as hazard-ratios (HR) with 95% confidence intervals. All analyses were conducted using SAS software (version 9.1; SAS Institute, Cary, NC).

Results

Population

Out of the 222 patients identified as included in the Mapp-prono study in the ENS@T database, causes of exclusion were: diagnosis of metastatic disease before 1998 or after 2010 in 6 or 38 cases respectively, benign tumor in 1 case, and proximal metastatic lymph nodes only in 8 cases. . At the end, 169 patients were included.

The median time between initial diagnosis and T0 was 43 months (range 0-614). The metastases were diagnosed within the first year in 79 patients (47%). A delayed diagnosis was observed with a time since the initial diagnosis above 5 and 10 years in 47 (28%) and 26 (15%) of the patients respectively.

At T0, a slight predominance of male was found (55%) and the mean age of the cohort was 48 ± 16 years (range 10-80). The primary tumor was located in the adrenal in 90 patients (53%) and at extra-adrenal sites in 79 patients (47%) including abdomen/pelvis or thoracic/neck in 63 and 16 patients, respectively. Twenty-two patients (13%) had multiple primaries. Ninety-four patients (57%) had tumor-related symptoms at presentation and 96 had hormone-related symptoms (58%). Fifty-three patients (32%) presented both tumor and hormone-related symptoms at T0 whereas 29 (17%) had no symptoms. Hormonal secretion as defined by an excess of Chromogranin A and or metanephrine/normetanephrine (MN/NMN) was reported in 117 out of 145 patients evaluable (81%) and elevated MN/NMN were found in 100 patients (72%). The size of the primary was available for 144 patients and was above 5 centimeters in 109 of them (76%). In patients with available pathological reports, the mitotic count exceeded 3 per high-power field (HPF) in 22 out of 83 patients (27%) and Ki67 was measured as follow: between 2 and 10% in 19 (40%) and above 10% in 18 patients (38%) out of 47 patients .The bone was the most frequent site of metastases (64%) and 35 patients (21%) had isolated bone metastases at presentation. The others metastatic organs were: distant lymph nodes (40%), lung (29%) and liver (26%). Seventy-three patients (43%) had metastases in both bone and soft tissues whereas 61 patients (36%) had no bone metastases. Fludeoxyglucose-positron emission tomography (FDG-PET) was positive for 94 patients out of 98 (96%). Of the four patients with negative FDG-PET, 2 had a neurofibromatosis type 1 (NF1) and 2 have an apparently sporadic disease. Characteristics of patients according to their primary location are reported in Table 2: patients with malignant pheochromocytoma were characterized by less frequent genetic disease, tumor-related symptoms or bone metastasis as compared to malignant paraganglioma.

Genetic features of the cohort

A mutation of a gene encoding a succinate dehydrogenase subunit was found in 70 patients including 63 *SDHB* mutation carriers (42%), 6 *SDHD* mutation carriers and 1 *SDHC* mutation carrier. Others 69 patients (46%), defined as apparently sporadic underwent a negative genetic screening including at least *SDHB*. Four patients had a clinical history of NF1, 4 patients had a Von Hippel Lindau disease (VHL) and 3 a multiple endocrine neoplasia type 2 (MEN2). At the end, patients can be classified into different subgroups depending on the cluster according to the unsupervised classical transcriptomic classification described for paraganglioma with 75 patients belonging to cluster 1 (50%); 4% to cluster 2 and 46% with sporadic MPP (25). Main characteristics of patients according to their genetic status are reported in Table 3. Finally, the genetic status was unknown for 18 patients (11%). Patients with sporadic tumors were characterized by older age at T0, higher median time to T0, adrenal primary and soft tissue metastases only as compared to cluster 1 patients.

Prognostic factors for survival in the cohort

The median follow-up from T0 was 64 months (range 0.5-185). Median overall survival was 6.7 years and 5-year overall survival was 62%. Seventy-eight of the 92 deaths were reported as related to the MPP (85%). Because no difference between overall and specific survival analyses was found, parameters affecting overall survival only were reported as described in Table 4. At univariate analysis (Figure 1), head and neck paraganglioma, younger age, absence of or low hormonal secretion (under 5 time upper normal range) and low proliferative index (as defined by mitosis ≤ 3/10 HPF and or Ki67 ≤ 2%) were significantly associated with a better overall survival. Patients with MEN2 and NF1, but also proliferative

index were excluded from the multivariate analysis because of their small number (Table 4). At multivariate analysis hypersecretion (HR 3.02[1.65-5.55]; *p*:0.0004) was identified as independent significant prognostic factors of worst overall survival.

Discussion

To the best of our knowledge, this series is the largest cohort of adult patients with MPP. Our aim was to progress in the prognostic stratification of this heterogeneous groups of neuroendocrine tumors. Our results do not confirm *SDHB* mutations as a major prognostic parameter in MPP and suggest additional key molecular events involved in MPP tumor progression. Primary tumor location and genetics were found highly intricated with MPP characterization.

Our series confirm several critical characteristics of MPP patients that include a prolonged disease-free interval justifying lifelong follow-up especially in asymptomatic patients. We found *SDHB* mutation in 42% of cases and well balanced pheochromocytoma and paraganglioma origin as expected because of the lower rate of malignancy but higher frequency of pheochromocytoma. We also found frequent bone locations isolated in 22% of cases urging specific bone site screening. Furthermore, in our cohort, the primary size was above 5 cm in 76% of cases.

The five-year survival was 62% in the range of published series (4–7). Interestingly, the vast majority of deaths were classified as MPP-related and, no difference was found in between OS and DSS analysis, suggesting that overall survival constitute a valuable primary endpoint in this group of tumors. Highlighted prognostic parameters deserve further comments. First patients with head and neck paraganglioma by contrast with other paraganglioma locations were associated with improved prognosis in univariate analysis but also a trend was found in multivariate analysis. Our result suggests that primary location of MPP could be considered at the time of prognostic stratification in two separate categories: head and neck paraganglioma and pheochromocytoma/abdomen-pelvic paraganglioma. We do not confirm the pejorative prognostic role of paraganglioma site as compared to pheochromocytoma in MPP and suggest that paraganglioma location may cover different entities with various behaviors. Larger series are required to definitely validate this hypothesis. Second, as for other well differentiated neuroendocrine tumors, hypersecretion but not hormonal or tumor symptoms was found pejorative. These biomarkers may be considered as reliable surrogates of both the secretory activity of the tumor but also the tumor burden. The efficacy of systemic but also local therapeutic options including surgery in reducing these secretions remains to be further explored. In line with that comment, the fact that the tumor burden as pointed out by the number or type of metastasized organs did not emerge as a prognostic parameter in our study is intriguing and may suggest insufficient tumor characterization in centers, still. Indeed, all patients underwent a thoracic abdominal and pelvic imaging but information on TEP imaging is missing in 58% of them. Third, genetics was found prognostic as defined by a worse prognosis of sporadic MPP. *SDHB* status was analyzed in 151 out of 169 patients (89%). Half of the patients with MPP harbor a mutation belonging to the cluster 1. That *SDHB* mutation rate is conformed to the other published series. But, in line with recent publications in the field, we do not confirm a prognostic role of *SDHB* mutation, which remains questionable. Indeed, *SDHB* was initially considered a risk factor for malignancy and secondly hypothesized as potentially carrying a prognostic value. Our results suggest that these two roles could be dissociated and additional molecular markers of tumor aggressiveness involved beyond *SDHB* mutation. However, confounding factors of this reasoning should be kept in mind: *SDHB* patient characteristics were associated with other favorable prognostic factors such as: younger age, earlier diagnosis, lower tumor burden at diagnosis but also more frequent head and neck

paraganglioma and absence of hypersecretion. In addition, *SDHB* patients may respond better to systemic therapy and benefit from a better surveillance screening. We also observe a trend for a better prognosis for patients with prolonged disease free interval and low Ki67. Both parameters constitute markers of tumor growth velocity that may constitute useful additional factors at the time of the therapeutic decision. As proposed in one earlier study, we therefore propose to evaluate the spontaneous radiological tumor rate of progression, as a surrogate of disease free interval, but also proliferative index in future prognostic studies (4).

Limitations of our study include the absence of functioning imaging in all patients, absence of consistent analysis of proliferative index and also metoxytyramine evaluation. In addition, the scarcity and retrospective nature of our study constitute well known limitations when evaluating rare cancers.

To conclude, MPP patients with sporadic disease and hypersecretion experienced a worst overall survival. Head and neck paraganglioma, may constitute a new favorable prognostic category. We recommend that treatments should aim at reducing the "secretory burden". The prognostic relevance of *SDHB* mutation is challenged. Efforts to implement international cohorts of well characterized MPP patients should be done to progress in the prognostic stratification.

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Disclosure summary:
The authors have declared no conflicts of interest

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Figure 1: Overall survival of MPP Patients according to (A) Primary location (B) Age at T0 (C) Disease free interval (D) Genetic status (E) Hormonal secretion and (F) Proliferative index. Cluster 1 genetic status includes patients with a *SDH*x or *MDH2* mutation and VHL disease; cluster 2 genetic status includes patients with MEN2 and NF1. Hypersecretion is defined as high if CgA and/or metanephrines > 5N; Proliferative index is defined as high if mitosis count is > 3/10 HPF and/or Ki67 > 2%.

Table 1: Demographics and baseline characteristics of patients at T0

Characteristics	*N* evaluable *n* (%)	Total *n* (%)
Number		169

Sex ratio (M/F)	169 (100)	93/76 (55/45)
Age at T0	169 (100)	48 years ± 16
Primary tumor site	169 (100)	
adrenal		90 (53)
extra-adrenal		79 (47)
Tumor-related symptoms	169 (100)	94 (57)
Hormones-related symptoms	169 (100)	96 (58)
Hypersecretion *	145 (86)	117 (81)
Pathology		
Size > 5 cm	144 (85)	109 (76)
Mitotic count > 3/10 HPF	83 (49)	22 (27)
Ki 67		
2-10%		19 (40)
>10%	47 (28)	18 (38)
Time between initial diagnosis and malignancy	169 (100)	
M1 within a year		79 (47)
M1 > 5 year		47 (28)
Metastatic site	169 (100)	
Bones		108 (64)
Lymph nodes		67 (40)
Lung		49 (29)
Liver		44 (26)
	98 (58)	94 (96)
FDG-PET		
Positive		
Genetics	151 (89)	
No mutation		69 (46)
NF1 clinical screening		4
MEN2		3
VHL		4
SDHB		63 (42)
SDHC		1
SDHD		6
MDH2		1

Figures represent the number of evaluable patients (%) or means ± SD.
*Hypersecreting tumor is defined as CgA and/or metanephrines > 2N

Table 2: Characterization of patients according to the primary

Characteristics	Adrenal *N* (%)	AbdoP PGL *N* (%)	HN PGL *N* (%)
N	90	63	16
Male	66 (73)	35 (56)	6 (37)
Age at T0 (year)	48,2	48,3	47,2
M1 < 1 year	39 (43)	33 (52)	7 (44)
Genetics			
N evaluable	76	59	16
Sporadic	52 (68)	13 (21)	4 (25)
SDHB	12 (13)	42 (67)	9 (56)
SDHC / SDHD / MDH2	0 / 1 / 0	1 / 2 / 1	0 / 3 / 0
VHL / MEN2 / NF1	4 / 3 / 4	0	0
Tumor-related syndrome	41/87 (47)	40 (63)	13 (81)
Hormone-related syndrome	53/87 (61)	39 (62)	4 (25)
Hypersecretion*	71/80 (89)	42/53 (79)	3/12 (25)
Metastases			
Bone only	14 (16)	15 (24)	6 (37)
Soft tissue only	49 (54)	19 (30)	5 (31)

Figures represent the number of evaluable patients (%), means ± SD, or median [IQR].
*Hypersecreting tumor is defined as CgA and/or metanephrines > 2N
AbdoP PGL: abdomino-pelvic paraganglioma; HN PGL: head and neck paraganglioma.

Table 3: Characterization of patients according to genetics

Characteristics	Cluster 1 *N* (%)	Sporadic *N* (%)	*p*
Number	75	69	
Males	38 (51)	40 (58)	NS
Age at T0 (years)	41 ± 16	53.8 ± 14	< **0.0001**

Median time to T0 (months)	4.1 [0-613]	26.9 [0-313]	**0.021**
M1 within a year	43 (58)	23 (33)	**0.004**
Primary tumor site			
adrenal	17 (23)	52 (75)	< **0.0001**
HN PGL	12 (16)	4 (6)	0.051
AbdoP PGL	46 (61)	13 (19)	< **0.0001**
multiples	15 (20)	5 (7)	**0.027**
Tumor-related symptoms	45 (60)	34 (49)	NS
Hormone-related symptoms	40 (53)	40 (58)	NS
Hypersecretion *	49 (65)	48 (70)	NS
Metastatic site			
Bone only	20 (27)	11 (16)	NS
Soft tissue only	20 (27)	43 (62)	< **0.0001**

Figures represent the number of evaluable patients (%), means ± SD, or median [IQR].
*Hypersecreting tumor is defined as CgA and/or metanephrines > 2N
AbdoP PGL: abdomino-pelvic paraganglioma; HN PGL: head and neck paraganglioma.

Table 4: Univariate and Multivariate Analysis of the association of prognostic factors with Overall Survival (OS)

Parameter	Univariate Analysis		Multivariate Analysis	
	HR [95% CI]	*P-value*	HR [95% CI]	*P-value*
Sex		0.62		
M	1			
F	1.11 [0.73-1.68]			
Primary		**0.023**		0.097
Adrenal	1		1	
Head and Neck	0.15 [0.04-0.62]		0.35 [0.07-1.62]	
Abdomino-pelvic	0.78 [0.51-1.2]		1.44 [0.8-2.59]	
Age at T0 (years)		**0.038**		0.13
< 40	1		1	
40-60	1.82 [1.07-3.09]		1.57 [0.84-2.92]	
> 60	2.12 [1.15-3.91]		2.08 [1.04-4.17]	
Disease free interval (years)		0.093		0.28
< 1	1		1	
1-5	1.02 [0.63-1.65]		0.77 [0.39-1.53]	
> 5	0.58 [0.34-0.98]		0.58 [0.3-1.14]	
Genetics		**<0.0001**		**0.53**
Sporadic and Cluster 2*	1		1	
Cluster 1	0.71 [0.44-1.13]		0.78 [0.38-1.62]	
Metastatic site		0.56		
Bone only	1			
Soft tissue only	0.81 [0.46-1.41]			
Both	1.02 [0.58-1.79]			
Nb of metastatic sites		0.18		
1	1			
2	0.72 [0.44-1.17]			
3	1.30 [0.74-2.3]			
4	1.37 [0.64-2.95]			
Tumor-related syndrome		0.70		
No	1			
Yes	1.20 [0.79-1.82]			
Unknown	1.02 [0.24-4.23]			
Hormone-related syndrome		0.95		
No	1			
Yes	0.94 [0.62-1.44]			
Unknown	0.89 [0.21-3.68]			
Hypersecretion		**0.0008**		**0.0004**
Absent or low	1		1	
High	2.42 [1.45-4.05]		3.02 [1.65-5.55]	
Proliferative index		**0.006**		0.19
Low	1		1	
High	2.39 [1.39-4.1]		2.07 [0.94-4.53]	

HR: hazard ratio, Hypersecretion is defined as high if CgA and/or metanephrines > 5N; Proliferative index is defined as high if mitosis count is > 3/10 HPF and/or Ki67 > 2%
*Cluster 2 patients were excluded for the multivariate analysis because of their small number.